P2-167 NSCLC: Combined Modality Therapy Posters, Tue, Sept 4

Induction docetaxel and cisplatin followed of bi-weekly docetaxel with concurrent thoracic radiotherapy for stage III non-small cell lung cancer (NSCLC). A phase II study conducted by the Galician Lung Cancer Group (GLCG).

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Background: The most satisfactory treatment for patients with locally advanced NSCLC is combination chemotherapy-radiotherapy (CT-RT). The optimal treatment modalities remain to be determined.

Methods: 60 patients (pts) with inoperable locally advanced NSCLC, stage IIIAN2/IIIB (no pleural T4), were included in a phase II study with induction chemotherapy consisting of three cycles of Docetaxel 75 mg/m^2 on D1 and Cisplatin 40 mg/m^2 D1-2 every 3 weeks and, if no surgery, then received concurrent CT-RT with Docetaxel 30 mg/m^2 every 2 weeks for four courses, during thoracic conformal radiotherapy (60-66 Gys, 180 cGy/day). The primary objective: overall survival; secondary: progression free survival, response rate (RR) and toxicity. Median follow-up: 9.1 mo.

Results: The pts characteristics were: mean age 62.9 yrs (43-74); male/female: 56/4; ECOG 0/1 in 17/43 pts; stage IIIAN2: 17 pts (28.3%) and stage IIIB 43 pts (71.7%). 56 pts were evaluables for response and 58 pts for toxicity. Induction chemotherapy response: 1 CR and 34 PR (RR 62.5%; CI95%:50-75), 16 SD (28.6%) and 5 PD (8.9%). 6 pts went to surgery: 3 pPR, 1 pSD, 1 pPD and 1 unresectable. 34 pts completed concurrent CT-RT treatment with 6 CR, 21 PR, 4 SD and 3 PD (RR 79.3%; CI95%:66-93). The median time to progression was 13 mo and median overall survival was 14 mo. The progression-free survival and overall survival at 1 year was 52% and 62% respectively. A total of 163 cycles of induction chemotherapy were administered (2.8 per pts), with the main toxicity (NCI-CTC) per pts Grade (g) 1-2/3-4 (%) was as follows: neutropenia 20.6/24.1; anemia 44.8/1.7; nausea/vomiting 39.6/1.7; fatigue 34.5/1.7; diarrhea 22.4/0; allergy 5.2/1.7; one toxic death were scored. The main toxicities (RTOG) in concurrent CT-RT were: g1-2 neutropenia/anemia 30.7/38.4 5% of pts; g1-2/3 esophagitis in 51.2/2.5% and g1-2/3 pneumonitis in 20.5/2.5 % of pts.

Conclusions: Docetaxel and Cisplatin induction chemotherapy followed by bi-weekly docetaxel with concurrent thoracic radiotherapy is a feasible treatment option, showing good clinical activity and tolerability for locally advanced NSCLC.

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Is 2D versus 3D planning detrimental for local control and survival in preoeperative radiochemotherapy in NSCLC?

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Background: We carried out a phase II trial to evaluate a regimen of polychemotherapy delivered concurrently with accelerated modified hyperfracctionated radiotherapy (AMHR) in NSCLC stage III patients. A subanalysis was made of the impact of planning method (2D versus 3D) on local control and overall survival.

Methods: Thirty eight patients (pts) received neoadjuvant therapy consisting of AMHR 40.2 Gy over 3 weeks (1,8 +0,88 Gy, by concomitant boost), concurrent with the second cycle of chemotherapy using cisplatin 80 ml/m^2 on day 1, ifosfamide 1.5 gr/m^2 on day 1 and VP-16 100 mg/m^2 for 3 days.

Results: From October 1997 to October 2002, 38 pts were treated. The most frequent cell type was squamous cell carcinoma, 20 (54%), and adenocarcinoma 11, (30%). From 1997 to June 1999, 17 pts were prepared with 2D. After this date 21 pts were done with 3D. Clinical response to CRT at restaging was observed in 30 pts (79%). One pt (3%) had complete response, 16 pts (42%) partial response, 13 (34%) stable disease and 4 pts (8%) developed progression. Surgery included pneumonectomy (n=14), bilobectomy (n=1) and lobectomy (n=14) and exploratory thoracotomy (n=1). Pathologic examination of the resected tissue demonstrated no residual viable tumor, (pathologic CR) in 13 / 28 completely resected pts (45%). Clinical response of pts with pCR when evaluated before surgery was partial in 8, stable disease in 4 and complete response in one. Overall 20 (69%) pts had sterilization of mediastinal lymph nodes and downstaging .There was 1 surgically-related death. Maximum toxicity was: esophagitis grade II in 8 pts (22%) and III in 1 pt (3%), neutropenia grade III -IV in 24%, thrombocytopenia grade III-IV in 13% and anemia grade III-IV in 10.5%. Twelve pts (32%) required hospitalisation due to toxicity. Stratified by type of planning disease free survival differed with more local control in the 2D arm (16 months for 2D versus 11.91months with 3D) but without statistical significance. Overall survival was also equivalent.

Median survival for the whole series was 22 months with survival at 5 years being 21.38 %. Median and 5 - year survival for patients who did or did not undergo surgery were 26.5 months, 35% and 8 months and 0%, respectively .

Conclusions: In this neoadjuvant radiochemotherapy treatment the type of planning (2D versus 3D) is not significantly detrimental on local control or overall survival although a trend to lesser local control has been detected in pts prepared for 3D. This trend may be due to the learning curve and a lack of planning norms such as published by Senan et al in 2004.

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Carboplatin and Gemcitabine as adjuvant therapy in completely resected stage I-IIIA non small cell lung cancer patients

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Purpose: To evaluate the efficacy, toxicity and compliance associated with adjuvant Carboplatin and Gemcitabine (CBDCA - GEM) administration in completely resected patients with stage I - IIIA non-small lung cancer (NSCLC)

Patient and Methods: Twenty-four patients with completely resected stage I-IIIA non-small lung cancer were administered 3 cycles of adjuvant chemotherapy consisting of carboplatin at an AUC of 4 and gemcitabine at dose 1000mg/m^2 on day 1 and 15, in a 4-week cycle. Patients' average age was 56.5 years and 96% of patients had ECOG performance status 0; 41.6% had pathological stage IIIA and 58.4% stage IB and II. Histologic tumor subtype was: 62.5% adenocarcinoma, 33.3% squamous cell carcinoma and 4.1% large-cell undifferentiated carcinoma.

Results: All patients enrolled in the study received the planned 3 cycles of adjuvant chemotherapy (compliance 100%). Myelotoxicity of all grades was observed in 8(33.3%) patients; grade 1-2 anemia in 7(29%), grade 1-3 thrombocytopenia in 2(8.3%) and grade 1 leucopenia in 1(4.1%). G-CSF at dose 33.6miu/day s.b. was administered on D4-D6 and D18-D20 of each cycle. Non-hematologic toxicity consisted of all grade nausea/vomiting(12.5%) and all grade diarrhea(8.3%). No treatment-related death was observed. The 2-year survival rate was 87.5%, and especially for stage IIIA patients 70%. A 5-year follow-up is ongoing.

Conclusions: We identified a comparable efficacy of adjuvant Carboplatin+Gemcitabine combination regimen with the one observed with Cisplatin-based chemotherapy regimens, however exhibiting a better toxicity profile and a high standard of compliance.

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Twice a day radiation therapy concomitant chemotherapy in locally advanced non small cell lung cancer

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Background: Combination of chemotherapy and thoracic radiation therapy is the best available treatment for locally advanced unresectable NSCLC. Results of conventional RT and CT are still not up to the acceptable level. We conducted a trial to compare chemotherapy given concurrently with twice daily external radiotherapy and conventional external radiotherapy alone in locally advanced NSCLC.

Methods: Fifty patients of locally advanced unresectable NSCLC were inducted into two arms, A & B. Twenty five patients of arm-A received chemotherapy with Cisplatin 75mg/m^2 intravenously given starting on day 1 of radiation therapy for 5 courses at 3 weeks interval and vinblastine 5mg/m^2 given weekly for 5 courses starting on day 1 of radiation along with twice daily external thoracic radiation therapy. The radiation was given twice daily at a dose of 1.3 Gy per fraction with each fraction separated by a minimum of 6 hours. A total dose of 60 Gy in 46 fractions over 4 weeks and 3 days was delivered. Twenty five patients of arm-B received only conventional external radiotherapy 60Gy in 30 fractions, 5 days a week over 6 weeks.

Results: Six weeks after the completion of treatment 67% of the patients in arm A showed some tumor response (27% CR; 40% PR) as compared to only 42% patients in the arm B. The only severe toxicities observed were leucopenia (5 patients in arm A) and esophagitis, grade 3 (4 patients in the arm A and 3 patients in arm B). At one year the survival rates were 61% in arm A and 39% in the arm B. No patient required hospitalization due to treatment related toxicity.

Conclusion: To conclude, hyper fractionated radiotherapy and chemotherapy regimen has promising efficacy and manageable toxicity in unresectable advanced NSCLC.

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Phase II and pharmacokinetic (PK) study of induction docetaxel/cisplatin followed by pulsed docetaxel chemoradiation for stage III non-small cell lung cancer

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Background: Both local and distant failure rates are high for inoperable NSCLC treated by combination chemoradiation (CRT). We have previously reported that docetaxel (Doc) demonstrates longer G2/M arrest and better sub-additive effects with radiation when compared with paclitaxel in pre-clinical investigations. We subsequently reported a clinical study using pulsed low-dose paclitaxel radiosensitizing strategy, which yielded a 98% in-filed chest tumor control rate [Clin Cancer Res, 9: 969-975, 2003]. With the encouraging local tumor control by pulsed taxane CRT, we conducted a phase II study using pulsed low-dose sensitizing Doc CRT targeting local tumor, plus one-cycle of induction chemotherapy (CT) of Doc/cisplatin (CP) targeting distant micrometastasis upfront for patients (pts) with stage III NSCLC.

Methods: Pts with inoperable stage III NSCLC were eligible. Induction CT consisted of Doc 75mg/m^2 and CP 75mg/m^2 on d 1 followed by rhG-CSF (150 ug/m^2 sq on d 2 to 10). The CRT consisted of Doc 12 mg/m^2 twice/wk with daily RT, 64.8 Gy to gross tumors and 45-57.6 Gy to subclinical disease. PK studies of Doc were performed during CT and during CRT in each pt. The clearance (CL), area under the plasma concentration versus time curve (AUC), and drug half-life (t1/2) were estimated.

Results: 26 pts were enrolled and 16 completed study. Overall response rate was 69% [50% (8/16) PR and19% (3/16) CR]. 2-year survival was 57 %. During induction CT, primary grade (G) 3 toxicities were allergic reaction (10%), non-neutropenic infection (20%), nausea/vomiting (N/V) (10%), fatigue (10%), hypertension (5%) hyperglycemia (5%), dyspnea (5%) & fatigue (5%). There was no G3/4 hematologic toxicity. During CRT, 50% (4/8) developed grade 3 esophagitis at the initial twice-weekly Doc dose of 12 mg/m^2. Eight subsequent pts received reduced Doc to 10 mg/m^2 with only one grade 3 esophagitis. Other G3 toxicities from CRT were N/V(28%), fatigue(14%), anorexia(14%), flushing(7%), chest pain(7%), & diarrhea(7%). We observed no G3 or 4 pneumonitis or any other G4 toxicity. Mean ± SD of Doc CL at 75 and 10 mg/m^2 was 20 ± 5 and 22 ± 10 L/h/m^2, respectively. Ratio of Doc CL at 75 to 10 mg/m^2 within a pt was 1.0 ± 0.4. Doc AUC at 75 and 10 mg/m^2 was 3,933 ± 1,028 and 566 ± 257ng/ml•h, respectively, with a ratio of 8.31 ± 3.84 for 75 mg/m^2 to 10 mg/m^2. Half-life of Doc at 75 and 10 mg/m^2 was 15.4 ± 3.7 hrs and 15.0 ± 2.2 hrs, respectively, with a ratio of 1.08 ± 0.15.

Conclusions: One-cycle full-dose Doc/CP with rhG-CSF followed by pulsed low-dose Doc CRT is associated with promising antitumor activity and low hematologic toxicity. Grade 3 esophagitis was associ-